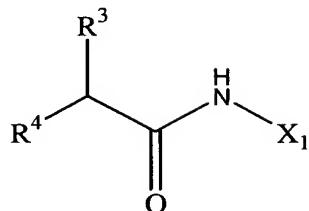


WE CLAIM:

1. A compound of Formula I:

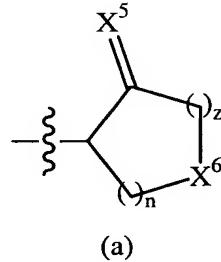


5

in which:

X^1 is $-C(R^1)(R^2)X^2$ or $-X^3$;
 X^2 is cyano, $-CHO$, $-C(R^7)(R^8)R^5$, $-C(R^7)(R^8)CF_3$, $-C(R^7)(R^8)CF_2CF_2R^9$
10 $-CH=CHS(O)_2R^5$, $-C(R^7)(R^8)CF_2C(O)NR^5R^6$, $-C(R^7)(R^8)C(R^7)(R^8)NR^5R^6$,
 $-C(R^7)(R^8)C(R^7)(R^8)OR^5$, $-C(R^7)(R^8)CH_2OR^5$, $-C(R^7)(R^8)CH_2N(R^6)SO_2R^5$,
 $-C(R^7)(R^8)C(R^7)(R^8)N(R^6)(CH_2)_2OR^6$, $-C(R^7)(R^8)C(R^7)(R^8)N(R^6)(CH_2)_2NR^6$ or
 $-C(R^7)(R^8)C(R^7)(R^8)R^5$; wherein R^5 is (C_{1-4}) alkyl, (C_{6-10}) aryl(C_{0-6})alkyl,
hetero(C_{4-10})aryl(C_{0-6})alkyl, (C_{4-10}) cycloalkyl(C_{0-6})alkyl or
15 hetero(C_{4-10})cycloalkyl(C_{0-6})alkyl; R^6 is hydrogen or (C_{1-6}) alkyl; R^7 is hydrogen or
 (C_{1-4}) alkyl and R^8 is hydroxy or R^7 and R^8 together form oxo; R^9 is hydrogen, halo,
 (C_{1-4}) alkyl, (C_{5-10}) aryl(C_{0-6})alkyl or hetero(C_{5-10})aryl(C_{0-6})alkyl;
 X^3 represents a group of Formula (a):

20



in which n is 1 or 2, z is 0 or 1, X^5 is selected from NR^{10} , S or O, wherein R^{10} is hydrogen or (C_{1-6})alkyl, and X^6 is O, S or NR^{11} , wherein R^{11} is selected from hydrogen, (C_{1-6})alkyl, $-X^4C(O)OR^{12}$, $-X^4C(O)R^{13}$, $-X^4C(O)NR^{12}R^{12}$, $-X^4S(O)_2NR^{12}R^{12}$, $-X^4S(O)_2R^{14}$, $-R^{15}$, $-X^4S(O)_2R^{15}$, $-X^4C(O)R^{15}$, $-X^4C(O)OR^{15}$, $-X^4C(O)NR^{12}R^{15}$ and $-X^4S(O)_2NR^{12}R^{15}$, in which

5 X^4 is a bond or (C_{1-6})alkylene; R^{12} at each occurrence independently is hydrogen or (C_{1-6})alkyl; R^{13} is hydrogen, (C_{1-6})alkyl or halo-substituted(C_{1-6})alkyl, R^{14} is (C_{1-6})alkyl or halo-substituted(C_{1-6})alkyl and R^{15} is (C_{3-10})cycloalkyl(C_{0-6})alkyl, hetero(C_{3-10})cycloalkyl(C_{0-3})alkyl, (C_{6-10})aryl(C_{0-6})alkyl, hetero(C_{5-10})aryl(C_{0-6})alkyl, (C_{9-12})bicycloaryl(C_{0-6})alkyl or hetero(C_{8-12})bicycloaryl(C_{0-6})alkyl;

10 wherein within X^1 any cycloalkyl, heterocycloalkyl, aryl or heteroaryl may be substituted with 1 radical R^{20} selected from $-R^{15}$, $-X^4OR^{15}$, $-X^4SR^{15}$, $-X^4S(O)R^{15}$, $-X^4S(O)_2R^{15}$, $-X^4C(O)R^{15}$, $-X^4C(O)OR^{15}$, $-X^4OC(O)R^{15}$, $-X^4NR^{15}R^{12}$, $-X^4NR^{12}C(O)R^{15}$, $-X^4NR^{12}C(O)OR^{15}$, $-X^4C(O)NR^{15}R^{12}$, $-X^4S(O)_2NR^{15}R^{12}$, $-X^4NR^{12}S(O)_2R^{15}$, $-X^4NR^{12}C(O)NR^{15}R^{12}$ and $-X^4NR^{12}C(NR^{12})NR^{15}R^{12}$; and wherein X^1 and R^{20} may be

15 substituted further with 1 to 5 radicals independently selected from (C_{1-6})alkyl, cyano, halo, halo-substituted(C_{1-4})alkyl, nitro, $-X^4NR^{12}R^{12}$, $-X^4NR^{12}C(O)R^{12}$, $-X^4NR^{12}C(O)OR^{12}$, $-X^4NR^{12}C(O)NR^{12}R^{12}$, $-X^4NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^4OR^{13}$, $-X^4SR^{13}$, $-X^4C(O)OR^{12}$, $-X^4C(O)R^{13}$, $-X^4OC(O)R^{13}$, $-X^4C(O)NR^{12}R^{12}$, $-X^4S(O)_2NR^{12}R^{12}$, $-X^4NR^{12}S(O)_2R^{13}$, $-X^4P(O)(OR^{12})OR^{12}$, $-X^4OP(O)(OR^{12})OR^{12}$, $-X^4S(O)R^{14}$ and $-X^4S(O)_2R^{14}$ wherein X^4 , R^{12} ,

20 R^{13} , R^{14} and R^{15} are as defined above;

R^1 and R^2 are both fluoro; or

R^1 is hydrogen or (C_{1-6})alkyl and R^2 is selected from the group consisting of hydrogen, (C_{1-6})alkyl, cyano, $-X^4NR^{12}R^{12}$, $-X^4NR^{12}C(O)R^{12}$, $-X^4NR^{12}C(O)OR^{12}$, $-X^4NR^{12}C(O)NR^{12}R^{12}$, $-X^4NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^4OR^{13}$, $-X^4SR^{13}$, $-X^4C(O)OR^{12}$, $25 -X^4C(O)R^{13}$, $-X^4OC(O)R^{13}$, $-X^4C(O)NR^{12}R^{12}$, $-X^4S(O)_2NR^{12}R^{12}$, $-X^4NR^{12}S(O)_2R^{13}$, $-X^4P(O)(OR^{12})OR^{12}$, $-X^4OP(O)(OR^{12})OR^{12}$, $-X^4S(O)R^{14}$, $-X^4S(O)_2R^{14}$, $-R^{15}$, $-X^4OR^{15}$, $-X^4SR^{15}$, $-X^4S(O)R^{15}$, $-X^4S(O)_2R^{15}$, $-X^4C(O)R^{15}$, $-X^4C(O)OR^{15}$, $-X^4OC(O)R^{15}$, $-X^4NR^{15}R^{12}$, $-X^4NR^{12}C(O)R^{15}$, $-X^4NR^{12}C(O)OR^{15}$, $-X^4C(O)NR^{15}R^{12}$, $-X^4S(O)_2NR^{15}R^{12}$, $-X^4NR^{12}S(O)_2R^{15}$, $-X^4NR^{12}C(O)NR^{15}R^{12}$ and $-X^4NR^{12}C(NR^{12})NR^{15}R^{12}$, wherein X^4 , R^{12} ,

30 R^{13} , R^{14} and R^{15} are as defined above; or R^1 and R^2 taken together with the carbon atom to which both R^1 and R^2 are attached form (C_{3-8})cycloalkylene or hetero(C_{3-8})cycloalkylene;

wherein R^2 , said cycloalkylene and said heterocycloalkylene may be substituted further with 1 to 3 radicals independently selected from (C_{1-6})alkyl, cyano, halo, halo-substituted(C_{1-4})alkyl, nitro, $-X^4NR^{12}R^{12}$, $-X^4NR^{12}C(O)R^{12}$, $-X^4NR^{12}C(O)OR^{12}$, $-X^4NR^{12}C(O)NR^{12}R^{12}$, $-X^4NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^4OR^{13}$, $-X^4SR^{13}$, $-X^4C(O)OR^{12}$, $-X^4C(O)R^{13}$, $-X^4OC(O)R^{13}$, $-X^4C(O)NR^{12}R^{12}$, $-X^4S(O)_2NR^{12}R^{12}$, $-X^4NR^{12}S(O)_2R^{13}$, $-X^4P(O)(OR^{12})OR^{12}$, $-X^4OP(O)(OR^{12})OR^{12}$, $-X^4S(O)R^{14}$ and $-X^4S(O)_2R^{14}$, wherein X^4 , R^{12} , R^{13} and R^{14} are as defined above;

R^3 and R^4 are independently $-C(R^{16})(R^{17})X^7$, wherein R^{16} and R^{17} are hydrogen, (C_{1-6})alkyl or fluoro, or R^{16} is hydrogen and R^{17} is hydroxy and X^7 is selected from $-X^4NR^{12}R^{12}$, $-X^4NR^{12}C(O)R^{12}$, $-X^4NR^{12}C(O)OR^{12}$, $-X^4NR^{12}C(O)NR^{12}R^{12}$, $-X^4NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^4OR^{13}$, $-X^4SR^{13}$, $-X^4C(O)OR^{12}$, $-X^4C(O)R^{13}$, $-X^4OC(O)R^{13}$, $-X^4C(O)NR^{12}R^{12}$, $-X^4S(O)_2NR^{12}R^{12}$, $-X^4NR^{12}S(O)_2R^{13}$, $-X^4P(O)(OR^{12})OR^{12}$, $-X^4OP(O)(OR^{12})OR^{12}$, $-X^4S(O)R^{14}$, $-X^4S(O)_2R^{14}$, $-R^{15}$, $-X^4OR^{15}$, $-X^4SR^{15}$, $-X^4S(O)R^{15}$, $-X^4S(O)_2R^{15}$, $-X^4C(O)R^{15}$, $-X^4C(O)OR^{15}$, $-X^4OC(O)R^{15}$, $-X^4NR^{15}R^{12}$, $-X^4NR^{12}C(O)R^{15}$, $-X^4NR^{12}C(O)OR^{15}$, $-X^4C(O)NR^{15}R^{12}$, $-X^4S(O)_2NR^{15}R^{12}$, $-X^4NR^{12}S(O)_2R^{15}$, $-X^4NR^{12}C(O)NR^{15}R^{12}$ and $-X^4NR^{12}C(NR^{12})NR^{15}R^{12}$, wherein X^4 , R^{12} , R^{13} , R^{14} and R^{15} are as defined above;

wherein within one of R^3 or R^4 any cycloalkyl, heterocycloalkyl, aryl or heteroaryl may be substituted with 1 radical R^{21} selected from $-R^{15}$, $-X^4OR^{15}$, $-X^4SR^{15}$, $-X^4S(O)R^{15}$, $-X^4S(O)_2R^{15}$, $-X^4C(O)R^{15}$, $-X^4C(O)OR^{15}$, $-X^4OC(O)R^{15}$, $-X^4NR^{15}R^{12}$, $-X^4NR^{12}C(O)R^{15}$, $-X^4NR^{12}C(O)OR^{15}$, $-X^4C(O)NR^{12}R^{15}$, $-X^4S(O)_2NR^{15}R^{12}$, $-X^4NR^{12}S(O)_2R^{15}$, $-X^4NR^{12}C(O)NR^{15}R^{12}$ and $-X^4NR^{12}C(NR^{12})NR^{15}R^{12}$, wherein X^4 , R^{12} and R^{15} are as defined above; and wherein each of R^3 , R^4 and R^{21} may be substituted further with 1 to 5 radicals independently selected from (C_{1-6})alkyl, cyano, halo, halo-substituted(C_{1-4})alkyl, nitro, $-X^4NR^{12}R^{12}$, $-X^4NR^{12}C(O)R^{12}$, $-X^4NR^{12}C(O)OR^{12}$, $-X^4NR^{12}C(O)NR^{12}R^{12}$, $-X^4NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^4OR^{13}$, $-X^4SR^{13}$, $-X^4C(O)OR^{12}$, $-X^4C(O)R^{13}$, $-X^4OC(O)R^{13}$, $-X^4C(O)NR^{12}R^{12}$, $-X^4S(O)_2NR^{12}R^{12}$, $-X^4NR^{12}S(O)_2R^{13}$, $-X^4P(O)(OR^{12})OR^{12}$, $-X^4OP(O)(OR^{12})OR^{12}$, $-X^4S(O)R^{14}$ and $-X^4S(O)_2R^{14}$, wherein X^4 , R^{12} , R^{13} and R^{14} are as defined above; provided that only one bicyclic ring structure is present within each of R^3 or R^4 ; and provided that when X^2 is cyano and X^7 within one of R^3 or R^4 is $-X^4C(O)R^{13}$ or $-X^4C(O)R^{15}$, wherein X^4 is a bond, then X^7 within the other of R^3 or R^4 is limited to

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-X⁴SR¹⁵, -X⁴S(O)R¹⁵ and -X⁴S(O)₂R¹⁵, wherein R¹⁵ is (C₆₋₁₀)aryl(C₁₋₆)alkyl substituted with 1 to 5 radicals or hetero(C₅₋₁₀)aryl(C₀₋₆)alkyl optionally substituted with 1 to 5 radicals, wherein said radicals are independently selected from (C₁₋₆)alkyl, cyano, halo, halo-substituted(C₁₋₄)alkyl, nitro, -X⁴NR¹²R¹², -X⁴NR¹²C(O)R¹², -X⁴NR¹²C(O)OR¹²,
 5 -X⁴NR¹²C(O)NR¹²R¹², -X⁴NR¹²C(NR¹²)NR¹²R¹², -X⁴OR¹³, -X⁴SR¹³, -X⁴C(O)OR¹²,
 -X⁴C(O)R¹³, -X⁴OC(O)R¹³, -X⁴C(O)NR¹²R¹², -X⁴S(O)₂NR¹²R¹², -X⁴NR¹²S(O)₂R¹³,
 -X⁴P(O)(OR¹²)OR¹², -X⁴OP(O)(OR¹²)OR¹², -X⁴S(O)R¹⁴ and -X⁴S(O)₂R¹⁴, wherein X⁴, R¹²,
 R¹³ and R¹⁴ are as defined above, provided that the radical is not selected from only halo
 when R¹⁵ is (C₆₋₁₀)aryl(C₁₋₆)alkyl; and provided that when X² is cyano then X⁷ within R³
 10 and R⁴ is not -X⁴C(O)NR¹²R¹², -X⁴C(O)NR¹⁵R¹² or -X⁴C(O)NR¹⁸R¹⁹, wherein X⁴ is a bond
 and R¹⁸ and R¹⁹ together with the nitrogen atom to which they are attached form
 hetero(C₃₋₁₀)cycloalkyl or hetero(C₅₋₁₀)aryl;

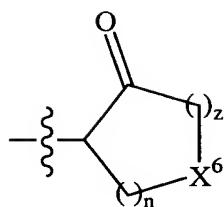
and the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof; and the pharmaceutically acceptable salts and
 15 solvates of such compounds and the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof.

2. The compound of Claim 1 in which:

X¹ is -C(R¹)(R²)X² or -X³;

20 X² is cyano, -CHO, -C(O)R⁵, -C(O)CF₃, -C(O)CF₂CF₂R⁹ -CH=CHS(O)₂R⁵,
 -C(O)CF₂C(O)NR⁵R⁶, -C(O)C(O)NR⁵R⁶, -C(O)C(O)OR⁵, -C(O)CH₂OR⁵,
 -C(O)CH₂N(R⁶)SO₂R⁵, -C(O)C(O)N(R⁶)(CH₂)₂OR⁶, -C(O)C(O)N(R⁶)(CH₂)₂NR⁶ or
 -C(O)C(O)R⁵, wherein R⁵ is (C₁₋₄)alkyl, (C₆₋₁₀)aryl(C₀₋₆)alkyl, hetero(C₄₋₁₀)aryl(C₀₋₆)alkyl,
 (C₄₋₁₀)cycloalkyl(C₀₋₆)alkyl or hetero(C₄₋₁₀)cycloalkyl(C₀₋₆)alkyl, R⁶ is hydrogen or
 25 (C₁₋₆)alkyl and R⁹ is halo;

X³ represents a group of Formula (b):



(b)

in which n is 1 or 2, z is 0 or 1, X⁶ is O or NR¹¹, wherein R¹¹ is selected from hydrogen, (C₁₋₆)alkyl, -X⁴OC(O)R¹³, -X⁴C(O)OR¹², -X⁴C(O)R¹³, -X⁴C(O)NR¹²R¹², -X⁴S(O)₂NR¹²R¹²,
 5 -X⁴S(O)₂R¹⁴, -R¹⁵, -X⁴S(O)₂R¹⁵, -X⁴C(O)R¹⁵, -X⁴C(O)OR¹⁵, -X⁴C(O)NR¹²R¹⁵ and -X⁴S(O)₂NR¹²R¹⁵, in which X⁴ is a bond or (C₁₋₆)alkylene; R¹² at each occurrence independently is hydrogen or (C₁₋₆)alkyl; R¹³ is hydrogen, (C₁₋₆)alkyl or halo-substituted(C₁₋₆)alkyl, R¹⁴ is (C₁₋₆)alkyl or halo-substituted(C₁₋₆)alkyl and R¹⁵ is (C₃₋₁₀)cycloalkyl(C₀₋₆)alkyl, hetero(C₃₋₁₀)cycloalkyl(C₀₋₃)alkyl, (C₆₋₁₀)aryl(C₀₋₆)alkyl,
 10 hetero(C₅₋₁₀)aryl(C₀₋₆)alkyl, (C₉₋₁₂)bicycloaryl(C₀₋₆)alkyl or hetero(C₈₋₁₂)bicycloaryl(C₀₋₆)alkyl;

wherein within X¹ any cycloalkyl, heterocycloalkyl, aryl or heteroaryl may be substituted with 1 radical selected from -R¹⁵ and -X⁴C(O)R¹⁵; and wherein X¹ may be substituted further with 1 to 3 radicals independently selected from (C₁₋₆)alkyl, halo-substituted(C₁₋₄)alkyl, -X⁴NR¹²R¹², -X⁴OR¹³ and -X⁴S(O)₂R¹⁴, wherein X⁴, R¹², R¹³, R¹⁴ and R¹⁵ are as defined above;

R¹ and R² are both fluoro; or

R¹ is hydrogen or (C₁₋₆)alkyl and R² is selected from the group consisting of hydrogen, (C₁₋₆)alkyl, -X⁴OR¹³ and -R¹⁵; or R¹ and R² taken together with the carbon atom to which both R¹ and R² are attached form (C₃₋₈)cycloalkylene or hetero(C₃₋₈)cycloalkylene; wherein R² may be substituted further with (C₁₋₆)alkyl; wherein X⁴, R¹³ and R¹⁵ are as defined above;

R³ and R⁴ are independently -C(R¹⁶)(R¹⁷)X⁷, wherein R¹⁶ and R¹⁷ are hydrogen, (C₁₋₆)alkyl or fluoro, or R¹⁶ is hydrogen and R¹⁷ is hydroxy and X⁷ is selected from -X⁴SR¹³, -X⁴C(O)R¹³, -X⁴C(O)NR¹²R¹², -R¹⁵, -X⁴OR¹⁵, -X⁴SR¹⁵, -X⁴S(O)₂R¹⁵, -X⁴C(O)R¹⁵ and -X⁴C(O)NR¹⁵R¹², wherein X⁴, R¹², R¹³ and R¹⁵ are as defined above;

wherein within one of R^3 or R^4 any cycloalkyl, heterocycloalkyl, aryl or heteroaryl may be substituted with 1 radical selected from $-R^{15}$, $-X^4OR^{15}$, $-X^4SR^{15}$, $-X^4S(O)R^{15}$, $-X^4S(O)_2R^{15}$, $-X^4C(O)R^{15}$, $-X^4C(O)OR^{15}$, $-X^4OC(O)R^{15}$, $-X^4NR^{15}R^{12}$, $-X^4NR^{12}C(O)R^{15}$, $-X^4NR^{12}C(O)OR^{15}$, $-X^4C(O)NR^{12}R^{15}$, $-X^4S(O)_2NR^{15}R^{12}$, $-X^4NR^{12}S(O)_2R^{15}$, $-X^4NR^{12}C(O)NR^{15}R^{12}$ and $-X^4NR^{12}C(NR^{12})NR^{15}R^{12}$, wherein X^4 , R^{12} and R^{15} are as defined above; and wherein each of R^3 and R^4 may be substituted further with 1 to 5 radicals independently selected from (C_{1-6})alkyl, cyano, halo, halo-substituted(C_{1-4})alkyl, nitro, $-X^4NR^{12}R^{12}$, $-X^4NR^{12}C(O)R^{12}$, $-X^4NR^{12}C(O)OR^{12}$, $-X^4NR^{12}C(O)NR^{12}R^{12}$, $-X^4NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^4OR^{13}$, $-X^4SR^{13}$, $-X^4C(O)OR^{12}$, $-X^4C(O)R^{13}$, $-X^4OC(O)R^{13}$, $-X^4C(O)NR^{12}R^{12}$, $-X^4S(O)_2NR^{12}R^{12}$, $-X^4NR^{12}S(O)_2R^{13}$, $-X^4P(O)(OR^{12})OR^{12}$, $-X^4OP(O)(OR^{12})OR^{12}$, $-X^4S(O)R^{14}$ and $-X^4S(O)_2R^{14}$, wherein X^4 , R^{12} , R^{13} and R^{14} are as defined above;

wherein within one of R^3 and R^4 any cycloalkyl, heterocycloalkyl, aryl or heteroaryl may be substituted with 1 radical selected from $-R^{15}$ and $-X^4OR^{15}$; and wherein each of R^3 or R^4 may be substituted further by 1-5 radicals independently selected from (C_{1-6})alkyl, cyano, halo, halo-substituted(C_{1-4})alkyl, $-X^4NR^{12}C(O)OR^{12}$, $-X^4OR^{13}$, $-X^4C(O)OR^{12}$, $-X^4C(O)R^{13}$, $-X^4C(O)NR^{12}R^{12}$, $-X^4NR^{12}S(O)_2R^{13}$ and $-X^4S(O)_2R^{14}$, wherein X^4 , R^{12} , R^{13} , R^{14} and R^{15} are as defined above;

and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof; and the pharmaceutically acceptable salts and solvates of such compounds and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof.

3. A compound of claim 2 in which R^3 and R^4 are independently $-CH_2X^7$, wherein X^7 is selected from X^4SR^{13} , $-X^4C(O)R^{13}$, $-X^4C(O)NR^{12}R^{12}$, $-R^{15}$, $-X^4OR^{15}$, $-X^4SR^{15}$, $-X^4S(O)_2R^{15}$, $-X^4C(O)R^{15}$ and $-X^4C(O)NR^{15}R^{12}$, wherein X^4 is a bond or (C_{1-6})alkylene, R^{12} at each occurrence independently is hydrogen or (C_{1-6})alkyl, R^{13} is hydrogen, (C_{1-6})alkyl or halo-substituted(C_{1-6})alkyl, R^{14} is (C_{1-6})alkyl or halo-substituted(C_{1-6})alkyl and R^{15} is (C_{3-10})cycloalkyl(C_{0-6})alkyl, (C_{3-10})cycloalkyl(C_{0-6})alkyl, hetero(C_{3-10})cycloalkyl(C_{0-3})alkyl, (C_{6-10})aryl(C_{0-6})alkyl, hetero(C_{5-10})aryl(C_{0-6})alkyl, (C_{9-12})bicycloaryl(C_{0-6})alkyl or

hetero(C₈₋₁₂)bicycloaryl(C₀₋₆)alkyl; wherein within R³ and R⁴ any cycloalkyl, heterocycloalkyl, aryl or heteroaryl may be substituted with 1 radical selected from -R¹⁵ and -X⁴OR¹⁵, wherein X⁴ and R¹⁵ are as defined above; and wherein R³ and R⁴ may be substituted further by 1 to 5 radicals independently selected from (C₁₋₆)alkyl, cyano, halo, 5 halo-substituted(C₁₋₄)alkyl, -X⁴NR¹²C(O)OR¹², -X⁴OR¹³, -X⁴C(O)OR¹², -X⁴C(O)R¹³, -X⁴C(O)NR¹²R¹², -X⁴NR¹²S(O)₂R¹³ and -X⁴S(O)₂R¹⁴, wherein X⁴ R¹², R¹³ and R¹⁴ are as defined above;

and the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof; and the pharmaceutically acceptable salts and 10 solvates of such compounds and the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof.

4. A compound of claim 3 in which R³ is selected from 5-bromo-thiophen-2-ylmethyl, 3-cyclohexylpropyl, 2-cyclohexylpropyl, 2-cyclopentylpropyl, 3-phenylpropyl, 15 3-(2-difluoromethoxy)phenylpropyl, 2-phenylcyclopropylmethyl, 2,2-difluoro-3-phenylpropyl, 1-benzylcyclopropylmethyl, 2-tetrahydro-pyran-4-ylethyl, 1-isobutylcyclopropylmethyl, thiophen-2-ylmethyl, tetrahydro-pyran-4-ylmethyl, cyclopropylmethylsulfanyl methyl, 2,2-dimethyl-3-phenylpropyl, 4-methyl-[1,2,5]thiadiazol-3-ylmethylsulfonylmethyl, 3-methyl-[1,2,4]thiadiazol-3-ylmethylsulfonylmethyl, thiophen-3-ylmethylsulfonylmethyl, 3-methoxy-5-methyl-isoxazol-4-ylmethylsulfonylmethyl, 2,4-dimethyl-thiazol-5-ylmethylsulfonylmethyl, 2-methyl-oxazol-4-ylmethylsulfonylmethyl, 2-methyl-thiazol-4-ylmethylsulfonylmethyl, 20 1,2,3]thiadiazol-4-ylmethylsulfonylmethyl, 3-methyl-[1,2,4]thiadiazol-5-ylmethylsulfonylmethyl, 4-methyl-[1,2,5]thiadiazol-3-ylmethylsulfonylmethyl, thiophen-3-ylmethylsulfonylmethyl, tetrahydro-pyran-4-yloxyethyl, piperidin-1-ylcarbonyl, 25 thiophene-2-sulfonylmethyl, 3-chloro-2-fluoro-benzylsulfonylmethyl, benzenesulfonylmethyl, benzylsulfonylmethyl, 2-(1,1-difluoro-methoxy)-benzylsulfonylmethyl, 2-benzenesulfonyl-ethyl, 2-(pyridine-2-sulfonyl)-ethyl, 2-(pyridine-4-sulfonyl)-ethyl, 2-benzylsulfonyl-ethyl, 30 oxy-pyridin-2-ylmethylsulfonylmethyl, prop-2-ene-1-sulfonylmethyl, 4-methoxy-benzylsulfonylmethyl, p-tolylmethylsulfonylmethyl,

	4-chloro-benzylsulfonylmethyl,	<i>o</i> -tolylmethylsulfonylmethyl,
	3,5-dimethyl-benzylsulfonylmethyl,	4-trifluoromethyl-benzylsulfonylmethyl,
	4-trifluoromethoxy-benzylsulfonylmethyl,	2-bromo-benzylsulfonylmethyl,
	pyridin-2-ylmethylsulfonylmethyl,	pyridin-3-ylmethylsulfonylmethyl,
5	pyridin-4-ylmethylsulfonylmethyl,	naphthalen-2-ylmethylsulfonylmethyl,
	3-methyl-benzylsulfonylmethyl,	3-trifluoromethyl-benzylsulfonylmethyl,
	3-trifluoromethoxy-benzylsulfonylmethyl,	
	4-fluoro-2-trifluoromethoxy-benzylsulfonylmethyl,	
	2-fluoro-6-trifluoromethyl-benzylsulfonylmethyl,	3-chloro-benzylsulfonylmethyl,
10	2-fluoro-benzylsulfonylmethyl,	2-trifluoro-benzylsulfonylmethyl,
	2-cyano-benzylsulfonylmethyl,	4- <i>tert</i> -butyl-benzylsulfonylmethyl,
	2-fluoro-3-methyl-benzylsulfonylmethyl,	3-fluoro-benzylsulfonylmethyl,
	4-fluoro-benzylsulfonylmethyl,	2-chloro-benzylsulfonylmethyl,
	2,5-difluoro-benzylsulfonylmethyl,	2,6-difluoro-benzylsulfonylmethyl,
15	2,5-dichloro-benzylsulfonylmethyl,	3,4-dichloro-benzylsulfonylmethyl,
	2-(1,1-difluoro-methoxy)-benzylsulfonylmethyl,	2-cyano-benzylsulfonylmethyl,
	3-cyano-benzylsulfonylmethyl,	2-trifluoromethoxy-benzylsulfonylmethyl,
	2,3-difluoro-benzylsulfonylmethyl,	2,5-difluoro-benzylsulfonylmethyl,
	biphenyl-2-ylmethylsulfonylmethyl,	cyclohexylmethyl,
20	3,4-difluoro-benzylsulfonylmethyl,	3-fluoro-benzylsulfonylmethyl,
	2,4,6-trifluoro-benzylsulfonylmethyl,	2,4-difluoro-benzylsulfonylmethyl,
	2,3,4-trifluoro-benzylsulfonylmethyl,	2,4,5-trifluoro-benzylsulfonylmethyl,
	2,5,6-trifluoro-benzylsulfonylmethyl,	2,3,5-trifluoro-benzylsulfonylmethyl,
	2-methyl-propane-1-sulfonyl,	2-chloro-5-trifluoromethylbenzylsulfonylmethyl,
25	2-fluoro-4-trifluoromethylbenzylsulfonylmethyl,	2-fluoro-3-trifluoromethylbenzylsulfonylmethyl,
	2-fluoro-5-trifluoromethylbenzylsulfonylmethyl,	
	4-fluoro-3-trifluoromethylbenzylsulfonylmethyl,	2-methoxy-benzylsulfonylmethyl,
	2-bis-trifluoromethyl-benzylsulfonylmethyl,	3,5-difluoromethoxy-benzylsulfonylmethyl,
	2-difluoromethoxy-benzylsulfonylmethyl,	3-difluoromethoxy-benzylsulfonylmethyl,
30	2,6-dichloro-benzylsulfonylmethyl,	biphenyl-4-ylmethylsulfonylmethyl,
	3,5-dimethyl-isoxazol-4-ylmethylsulfonylmethyl,	

5-chloro-thiophen-2-ylmethylsulfonylmethyl,
 2-[4-(1,1-Difluoro-methoxy)-benzenesulfonyl]-ethyl,
 2-[2-(1,1-Difluoro-methoxy)-benzenesulfonyl]-ethyl,
 2-[3-(1,1-Difluoro-methoxy)-benzenesulfonyl]-ethyl,
 5 2-(4-trifluoromethoxy-benzenesulfonyl)-ethyl,
 2-(3-trifluoromethoxy-benzenesulfonyl)-ethyl,
 2-(2-trifluoromethoxy-benzenesulfonyl)-ethyl, (cyanomethyl-methyl-carbamoyl)-methyl,
 biphenyl-3-ylmethyl, 2-oxo-2-pyrrolidin-1-yl-ethyl, 2-benzenesulfonyl-ethyl,
 isobutylsulfanyl methyl, 2-phenylsulfanyl-ethyl, cyclohexylmethylsulfonylmethyl,
 10 2-cyclohexyl-ethanesulfonyl, benzyl, naphthalen-2-yl, benzylsulfanyl methyl,
 2-trifluoromethyl-benzylsulfanyl methyl, phenylsulfanyl-ethyl and
 cyclopropylmethylsulfonylmethyl;

and the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof; and the pharmaceutically acceptable salts and 15 solvates of such compounds and the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof.

5. A compound of claim 4 in which R^4 is selected from
 2-trifluorobenzylsulfonylmethyl, 3-phenylsulfanylpropyl, 4-chlorobenzylsulfonylmethyl,
 20 thiophen-2-ylsulfonylmethyl, benzylsulfonylmethyl, 4-methylbenzylsulfonylmethyl,
 2-phenylsulfonylethyl, 2-pyridin-2-ylsulfonylethyl, 2-pyridin-4-ylsulfonylethyl,
 2-benzylsulfonylethyl, 2-(3-difluoromethoxyphenylsulfonyl)ethyl,
 naphthalen-2-ylmethylsulfonylmethyl, pyridin-2-ylmethylsulfonylmethyl,
 3-methylbenzylsulfonylmethyl, 3-trifluoromethylbenzylsulfonylmethyl,
 25 3-difluoromethoxybenzylsulfonylmethyl, 3-chlorobenzylsulfonylmethyl,
 3-fluorobenzylsulfonylmethyl, 4-fluorobenzylsulfonylmethyl,
 3-cyanobenzylsulfonylmethyl, 4-cyanobenzylsulfonylmethyl,
 3,4-difluorobenzylsulfonylmethyl, benzylsulfonylmethyl,
 N-cyanomethyl-N-methylcarbamoylmethyl, 3-bromobenzyl, 4-phenylbutyl, 2,2-difluoro-
 30 3-phenylpropyl, 4'-methylsulfonylaminobiphenyl-3-ylmethyl,
 4'-ethoxycarbonylaminobiphenyl-3-ylmethyl, 4-methylpiperazin-1-ylcarbonylmethyl,

1-fluoro-2-(4-methylpiperazin-1-yl)-2-oxoethyl, 1-hydroxy-4-methylpiperazin-1-yl-2-oxoethyl, 1-hydroxy-2-morpholin-4-yl-2-oxoethyl, 1-hydroxy-2-oxo-2-pyrrolidin-1-yl-ethyl, 1-fluoro-2-oxo-2-pyrrolidin-1-yl-ethyl, 1-fluoro-2-isopropylamino-2-oxoethyl, 1-hydroxy-2-isopropylamino-2-oxoethyl, 1-fluoro-2-oxo-2-piperazin-1-ylethyl,

5 thiophen-3-ylmethylsulfonylmethyl, 4-methyl-[1,2,5]thiadiazol-3-ylmethylsulfonylmethyl, 3-methoxy-5-methyl-isoxazol-4-ylmethylsulfonylmethyl, 2,4-dimethyl-thiazol-5-ylmethylsulfonylmethyl, 2-methyl-oxazol-4-ylmethylsulfonylmethyl, 2-methyl-thiazol-4-ylmethylsulfonylmethyl, 2-([1,2,3]thiadiazol-4-ylmethylsulfonyl)-ethyl, 2-(3-methyl-[1,2,4]thiadiazol-5-ylmethylsulfonyl)-ethyl, 2-oxo-2-phenyl-ethyl,

10 2-morpholin-4-yl-2-oxo-ethyl, 2-benzenesulfonyl-ethyl, 2-naphthalen-2-yl-2-oxo-ethyl, 2-benzo[1,3]dioxol-5-yl-2-oxo-ethyl, 2-benzo[b]thiophen-2-yl-2-oxo-ethyl, 2-biphenyl-4-yl-2-oxo-ethyl, 4-benzylsulfonylmethyl, 2-(3-trifluoromethoxy-benzenesulfonyl)-ethyl, 2-oxo-2-(4-phenoxy-phenyl)-ethyl, 2-(4-hydroxy-phenyl)-2-oxo-ethyl, benzylcarbamoyl-methyl,

15 4-acetyl-piperazine-1-carboxylic acid ethyl ester, cyclohexylcarbamoylmethyl, 2-(3-Chloro-benzo[b]thiophen-2-yl)-2-oxo-ethyl, benzenesulfonylmethyl, 2-oxo-2-thiophen-2-yl-ethyl, 2-oxo-2-thiophen-3-yl-ethyl, naphthalene-2-sulfonylmethyl, 2-(5-methyl-thiophen-2-yl)-2-oxo-ethyl, 2-(3-chloro-thiophen-2-yl)-2-oxo-ethyl, 5-methyl-thiophene-2-sulfonylmethyl, phenylcarbamoylmethyl,

20 (5,6,7,8-tetrahydro-naphthalen-1-ylcarbamoyl)-methyl, (4-carbamoyl-phenylcarbamoyl)-methyl, (3-carbamoyl-phenylcarbamoyl)-methyl, (butyl-methyl-carbamoyl)-methyl, biphenyl-4-ylmethyl, 2-oxo-2-p-tolyl-ethyl, 2-(3-fluoro-4-methoxy-phenyl)-2-oxo-ethyl, 2-(4-chloro-phenyl)-2-oxo-ethyl, 2-(4-methoxy-phenyl)-2-oxo-ethyl, 2-oxo-2-(4-trifluoromethoxy-phenyl)-ethyl,

25 2-(3,4-difluoro-phenyl)-2-oxo-ethyl, 2-(3,4-dimethoxy-phenyl)-2-oxo-ethyl, 2-(4-fluoro-phenyl)-2-oxo-ethyl, 5-methyl-2-oxo-hexyl, 3,5-dimethyl-benzylsulfonylmethyl, 4-trifluoromethyl-benzylsulfonylmethyl; 4-trifluoromethoxy-benzylsulfonylmethyl, isopropylcarbamoyl-methyl, 4-dimethylcarbamoylmethyl, pyridin-4-ylcarbamoylmethyl,

30 pyridin-4-ylmethylsulfonylmethyl, pyridin-3-ylmethylsulfonylmethyl, 3,4-dichloro-benzylsulfonylmethyl, pyridin-3-ylcarbamoylmethyl,

4-methoxy-benzylsulfonylmethyl, 4-chloro-benzylsulfonylmethyl,
 thiophene-2-sulfonylmethyl, benzylsulfonylmethyl, *p*-tolylmethylsulfonylmethyl,
 2-benzenesulfonyl-ethyl, 2-(pyridine-2-sulfonyl)-ethyl, 2-(pyridine-4-sulfonyl)-ethyl,
 2-benzylsulfonyl-ethyl, 2-[3-(1,1-Difluoro-methoxy)-benzenesulfonyl]-ethyl,
 5 naphthalen-2-ylmethylsulfonylmethyl, pyridin-2-ylmethylsulfonylmethyl,
m-tolylmethylsulfonylmethyl, 3-trifluoromethyl-benzylsulfonylmethyl,
 3-trifluoromethoxy-benzylsulfonylmethyl, 3-chloro-benzylsulfonylmethyl,
 3-fluoro-benzylsulfonylmethyl, 4-fluoro-benzylsulfonylmethyl,
 3-cyano-benzylsulfonylmethyl, 4-cyano-benzylsulfonylmethyl,
 10 3,4-difluoro-benzylsulfonylmethyl, (cyanomethyl-methyl-carbamoyl)-methyl,
 3-bromo-benzyl, 2-oxo-2-pyrrolidin-1-yl-ethyl, 2-(4'-chloro-biphenyl-4-yl)-2-oxo-ethyl,
 biphenyl-3-ylmethyl, 2-(1,1-difluoro-methoxy)-benzylsulfonylmethyl,
 2-(4-methylsulfonylamino-phenyl)-2-oxo-ethyl, 2-oxo-2-piperidin-1-yl-ethyl,
 2-(4-methylsulfonyl-piperazin-1-yl)-2-oxo-ethyl, 2-trifluoromethyl-benzylsulfonylmethyl,
 15 4-fluoro-3-trifluoromethyl-benzylsulfonylmethyl, 4-carboxy-benzylsulfonylmethyl,
 3,5-bis-trifluoromethyl-benzylsulfonylmethyl,
 4-(1,1-difluoro-methoxy)-benzylsulfonylmethyl,
 3-(1,1-difluoro-methoxy)-benzylsulfonylmethyl,
 5-chloro-thiophen-2-ylmethylsulfonylmethyl,
 20 2-[4-(1,1-difluoro-methoxy)-benzenesulfonyl]-ethyl,
 2-(4-trifluoromethoxy-benzenesulfonyl)-ethyl, 2-phenylsulfanyl-ethyl,
 benzylsulfanyl methyl, 2-trifluoromethyl-benzylsulfanyl methyl,
 2-trifluoromethoxy-benzylsulfanyl methyl, 2-cyclohexyl-ethyl and isobutylsulfanyl methyl;
 and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual
 25 isomers and mixtures of isomers thereof; and the pharmaceutically acceptable salts and
 solvates of such compounds and the *N*-oxide derivatives, prodrug derivatives, protected
 derivatives, individual isomers and mixtures of isomers thereof.

6. The compound of claim 5 in which R¹ is hydrogen or (C₁₋₆)alkyl and R² is
 30 hydrogen, -X⁴OR¹³, hetero(C₅₋₁₀)aryl(C₀₋₆)alkyl, (C₅₋₁₀)aryl(C₀₋₆)alkyl or (C₁₋₆)alkyl; or R¹
 and R² taken together with the carbon atom to which both R¹ and R² are attached form

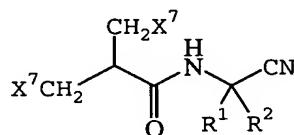
(C₃₋₈)cycloalkylene or hetero(C₃₋₈)cycloalkylene; wherein the cycloalkylene or heterocycloalkylene are optionally substituted with 1 to 3 (C₁₋₆)alkyl radicals;

and the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof; and the pharmaceutically acceptable salts and 5 solvates of such compounds and the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof.

7. The compound of claim 6 in which R¹ is hydrogen or methyl and R² is methoxymethyl, methoxyethyl, methyl, ethyl, propyl, butyl, phenethyl, hiophen-2-yl or 5-10 methyl-furan-2-yl; or R¹ and R² taken together with the carbon atom to which both R¹ and R² are attached form cyclopropyl, tetrahydro-pyran-4-yl or 1-methyl-piperidin-4-yl;

and the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof; and the pharmaceutically acceptable salts and solvates of such compounds and the N-oxide derivatives, prodrug derivatives, protected 15 derivatives, individual isomers and mixtures of isomers thereof.

8. The compound of claim 7 of Formula I(a):



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I(a)

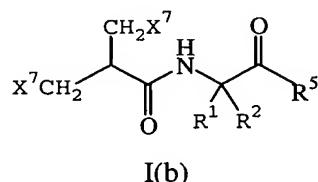
and the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof; and the pharmaceutically acceptable salts and solvates of 25 such compounds and the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof.

9. The compound of claim 8 selected from the group consisting of 3-biphenyl-3-yl-N-cyanomethyl-2-benzylsulfonylmethyl-propionamide; 3-biphenyl-4-yl-N-

cyanomethyl-2-benzylsulfonylmethyl-propionamide; 3-(3-bromo-phenyl)-*N*-cyanomethyl-2-benzylsulfonylmethyl-propionamide; *N*-cyanomethyl-3-(3-cyano-benzylsulfonyl)-2-benzylsulfonyl-methyl-propionamide; *N*-cyanomethyl-2-[2-(1,1-difluoro-methoxy)-benzylsulfanyl-methyl]-3-benzylsulfanyl-propionamide; *N*-cyanomethyl-3-(2-trifluoromethyl-benzylsulfanyl)-2-(2-trifluoro-methyl-benzylsulfanyl-methyl)-propionamide; *N*-cyanomethyl-3-isobutylsulfanyl-2-isobutylsulfanyl-methyl-propionamide; *N*-cyanomethyl-4-phenylsulfanyl-2-(2-phenylsulfanyl-ethyl)-butyramide; *N*-cyanomethyl-3-[2-(1,1-difluoro-methoxy)-benzylsulfanyl]-2-[2-(1,1-difluoro-methoxy)-benzylsulfanyl-methyl]-propionamide; 3-benzylsulfanyl-2-benzylsulfanyl-methyl-*N*-cyanomethyl-propionamide; *N*-cyanomethyl-2-[2-(1,1-difluoro-methoxy)-benzylsulfanyl-methyl]-3-benzylsulfanyl-propionamide; *N*-cyanomethyl-3-(2-trifluoromethyl-benzylsulfanyl)-2-(2-trifluoromethyl-benzylsulfanyl-methyl)-propionamide; 4-benzenesulfonyl-2-(2-benzenesulfonyl-ethyl)-*N*-cyanomethyl-butyramide; *N*-cyanomethyl-3-[2-(1,1-difluoro-methoxy)-benzylsulfanyl]-2-[2-(1,1-difluoro-methoxy)-benzylsulfanyl-methyl]-propionamide; *N*-cyanomethyl-3-benzylsulfonyl-2-benzylsulfanyl-methyl-propionamide; *N*-cyanomethyl-3-(2-methyl-propane-1-sulfonyl)-2-(2-methyl-propane-1-sulfonyl-methyl)-propionamide; *N*-cyanomethyl-3-(2-methyl-thiazol-4-ylmethylsulfonyl)-2-benzyl-sulfanyl-methyl-propionamide; 3-biphenyl-3-yl-*N*-cyanomethyl-2-[2-(1,1-difluoro-methoxy)-benzyl-sulfanyl-methyl]-propionamide; (3'-(2-(cyanomethyl-carbamoyl)-3-[2-(1,1-difluoro-methoxy)-benzyl-sulfonyl]-propyl)-biphenyl-4-yl)-carbamic acid ethyl ester; *N*-cyanomethyl-2-[2-(1,1-difluoro-methoxy)-benzylsulfanyl-methyl]-3-(4'-methylsulfonylamino-biphenyl-3-yl)-propionamide; 3-(3-bromo-phenyl)-*N*-cyanomethyl-2-[2-(1,1-difluoro-methoxy)-phenyl-methylsulfanyl-methyl]-propionamide; *N*-cyanomethyl-2-((E)-3-phenyl-allyl)-3-benzylsulfonyl-propionamide; and *N*-cyanomethyl-3-benzylsulfonyl-2-(3-phenyl-propyl)-propionamide;

and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof; and the pharmaceutically acceptable salts and solvates of such compounds and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof.

10. The compound of Claim 7 of Formula I(b):



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and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof; and the pharmaceutically acceptable salts and solvates of such compounds and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof.

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11. The compound of claim 10 in which R^5 is 1*H*-benzoimidazol-2-yl, benzooxazol-2-yl, oxazolo[4,5-*b*]pyridin-2-yl, benzothiazol-2-yl, 5-phenyl-[1,3,4]oxadiazol-2-yl, 4-(5-pyridin-4-yl-[1,3,4]oxadiazol-2-yl, 5-pyridin-3-yl-[1,3,4]oxadiazol-2-yl, 5-pyridazin-3-yl-[1,3,4]oxadiazol-2-yl, pyrimidin-2-yl, pyridazin-3-yl, 3-penyl-[1,2,4]oxadiazol-5-yl, 5-methoxymethyl-[1,3,4]oxadiazol-2-yl, 5-ethyl-[1,3,4]oxadiazol-2-yl, 1,3,4]thiadiazol-2-yl, benzyloxycarbonyl, benzyloxydicarbonyl, phenyldicarbonyl, 5-methyl-[1,3,4]thiadiazol-2-yl, 5-trifluoromethyl-[1,3,4]oxadiazol-2-yl, 5-methyl-[1,3,4]oxadiazol-2-yl, 5-methyl-[1,2,4]oxadiazol-3-yl, 5-phenyl-[1,2,4]oxadiazol-3-yl, 5-thiophen-3-yl-[1,2,4]oxadiazol-3-yl, 5-trifluoromethyl-[1,2,4]oxadiazol-3-yl, 3-methyl-[1,2,4]oxadiazol-5-yl or 3-pyrazin-2-yl;

and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof; and the pharmaceutically acceptable salts and solvates of such compounds and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof.

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12. The compound of claim 11 selected from the group consisting of *N*-(*S*)-1-(1-Benzooxazol-2-yl-methanoyl)-butyl]-3-benzylsulfonyl-2-benzylsulfonylmethyl-propionamide; *N*-(*S*)-1-(1-Benzooxazol-2-yl-methanoyl)-butyl]-3-(2-trifluoromethyl-benzylsulfonyl)-2-(2-trifluoromethyl-benzylsulfonylmethyl)-propionamide; *N*-(*S*)-1-(1-

[1-(oxazolo[4,5-b]pyridine-2-carbonyl)-propyl]-4-oxo-2-benzylsulfonylmethyl-butyramide; N-[1-(Oxazolo[4,5-b]pyridine-2-carbonyl)-propyl]-4-oxo-2-benzylsulfonyl-methyl-4-piperidin-1-yl-butyramide; N-[1-(Oxazolo[4,5-b]pyridine-2-carbonyl)-propyl]-4-oxo-2-benzylsulfonyl-methyl-4-pyrrolidin-1-yl-butyramide; 4-Morpholin-4-yl-4-oxo-2-benzylsulfonylmethyl-N-[1-(5-pyridin-4-yl-[1,3,4]oxadiazole-2-carbonyl)-propyl]-butyramide; 4-Oxo-2-benzylsulfonylmethyl-4-piperidin-1-yl-N-[1-(5-pyridin-4-yl-[1,3,4]oxadiazole-2-carbonyl)-propyl]-butyramide; 4-Oxo-2-benzylsulfonylmethyl-N-[1-(5-pyridin-4-yl-[1,3,4]oxadiazole-2-carbonyl)-propyl]-4-pyrrolidin-1-yl-butyramide; 4-Morpholin-4-yl-4-oxo-2-benzylsulfonylmethyl-N-[1-(5-pyridin-3-yl-[1,3,4]oxadiazole-2-carbonyl)-propyl]-butyramide; N-[1-(Benzooxazole-2-carbonyl)-propyl]-4-oxo-2-benzylsulfonylmethyl-4-piperidin-1-yl-butyramide; N-[1-(Benzooxazole-2-carbonyl)-propyl]-4-oxo-2-benzylsulfonylmethyl-4-pyrrolidin-1-yl-butyramide; N-[1-(Benzooxazole-2-carbonyl)-propyl]-2-cyclohexylmethyl-4-morpholin-4-yl-4-oxo-butyramide; 2-Cyclohexylmethyl-4-morpholin-4-yl-N-[1-(oxazolo[4,5-b]pyridine-2-carbonyl)-propyl]-4-oxo-butyramide; 2-Cyclohexylmethyl-N-[1-(5-ethyl-[1,3,4]oxadiazole-2-carbonyl)-butyl]-4-morpholin-4-yl-4-oxo-butyramide; N-(2-Benzooxazol-2-yl-1-methoxymethyl-2-oxo-ethyl)-2-(2-difluoromethoxy-benzylsulfonylmethyl)-4-morpholin-4-yl-4-oxo-butyramide; N-[1-(Benzooxazole-2-carbonyl)-propyl]-2-(2-cyclohexyl-ethyl)-4-morpholin-4-yl-4-oxo-butyramide; 2-(2-Cyclohexyl-ethyl)-4-morpholin-4-yl-N-[1-(oxazolo[4,5-b]pyridine-2-carbonyl)-propyl]-4-oxo-butyramide; 2-(2-Cyclohexyl-ethyl)-4-morpholin-4-yl-4-oxo-N-[1-(5-phenyl-[1,3,4]oxadiazole-2-carbonyl)-propyl]-butyramide; 2-(2-Difluoromethoxy-benzylsulfonylmethyl)-4-morpholin-4-yl-4-oxo-N-[1-(5-phenyl-[1,3,4]oxadiazole-2-carbonyl)-propyl]-butyramide; 2-(2-Difluoromethoxy-benzylsulfonylmethyl)-N-[1-(5-ethyl-[1,3,4]oxadiazole-2-carbonyl)-butyl]-4-morpholin-4-yl-4-oxo-butyramide; N-[1-(Benzooxazole-2-carbonyl)-propyl]-2-(2-difluoromethoxy-benzyl-sulfonylmethyl)-4-morpholin-4-yl-4-oxo-butyramide; 2-(2-Morpholin-4-yl-2-oxo-ethyl)-5-phenyl-pentanoic acid, 1-(benzooxazole-2-carbonyl)-propyl]-amide; (R)-2-Cyclohexylmethyl-4-morpholin-4-yl-4-oxo-N-[S]-1-(5-phenyl-1,2,4-oxadiazole-3-carbonyl)-propyl]-butyramide; 2-(2-Morpholin-4-yl-2-oxo-ethyl)-5-phenyl-pentanoic acid, (S)-1-(5-phenyl-[1,2,4]oxadiazole-3-carbonyl)-propyl]-amide; 4-Morpholin-4-yl-4-oxo-2-benzylsulfonylmethyl-N-[S]-1-(5-phenyl-1,2,4-

oxadiazole-3-carbonyl)-propyl]-butyramide; (R)-2-Cyclohexylmethyl-4-morpholin-4-yl-4-oxo-*N*-(*S*)-1-(3-phenyl-1,2,4-oxadiazole-5-carbonyl)-propyl]-butyramide; 4-Morpholin-4-yl-*N*-[1-(oxazole-2-carbonyl)-3-phenyl-propyl]-4-oxo-2-benzylsulfonylmethyl-butyramide; *N*-(1,1-Dimethyl-2-oxazol-2-yl-2-oxo-ethyl)-4-morpholin-4-yl-4-oxo-2-

5 benzylsulfonylmethyl-butyramide; *N*-4-Isopropyl-*N*-1-[1-(oxazole-2-carbonyl)-3-phenyl-propyl]-2-benzylsulfonylmethyl-succinamide; 2-(2-Difluoromethoxy-benzylsulfonylmethyl)-4-morpholin-4-yl-*N*-[1-(oxazole-2-carbonyl)-3-phenyl-propyl]-4-oxo-butyramide; 2-(2-Methyl-propane-1-sulfonylmethyl)-4-morpholin-4-yl-*N*-[1-(oxazole-2-carbonyl)-3-phenyl-propyl]-4-oxo-butyramide; 2-Cyclopropylmethylsulfonylmethyl-4-

10 morpholin-4-yl-*N*-[1-(oxazole-2-carbonyl)-3-phenyl-propyl]-4-oxo-butyramide; *N*-[1-(Benzooxazole-2-carbonyl)-butyl]-2-benzylsulfonyl-3-(tetrahydro-pyran-4-yloxyethyl)-propionamide; *N*-[1-(Benzooxazole-2-carbonyl)-butyl]-3-ethanesulfonyl-2-(tetrahydro-pyran-4-yloxyethyl)-propionamide; *N*-(1-Benzenesulfonyl-3-oxo-azepan-4-yl)-2-cyclopropylmethylsulfonyl-methyl-4-morpholin-4-yl-4-oxo-butyramide; 2-

15 Cyclopropylmethylsulfonylmethyl-*N*-{(*S*)-1-[*(R)*-hydroxy-(3-phenyl-1,2,4-oxadiazol-5-yl)-methyl]-propyl}-4-morpholin-4-yl-4-oxo-butyramide; *N*-{(*S*)-1-[*(R)*-hydroxy-(3-phenyl-1,2,4-oxadiazol-5-yl)-methyl]-propyl}-2-(2-methyl-propane-1-sulfonylmethyl)-4-morpholin-4-yl-4-oxo-butyramide; 2-(2-Morpholin-4-yl-2-oxo-ethyl)-5-phenyl-pentanoic acid {(*S*)-1-[*(R)*-hydroxy-(3-phenyl-1,2,4-oxadiazol-5-yl)-methyl]-propyl}-amide; 2-

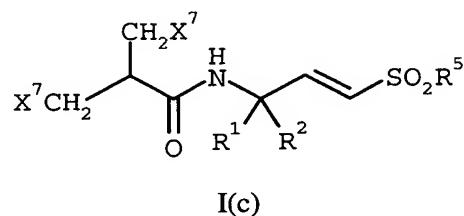
20 Cyclopropylmethylsulfonylmethyl-4-morpholin-4-yl-4-oxo-*N*-[*(S*)-1-(3-phenyl-1,2,4-oxadiazole-5-carbonyl)-propyl]-butyramide; 2-(2-methyl-propane-1-sulfonylmethyl)-4-morpholin-4-yl-4-oxo-*N*-[*(S*)-1-(3-phenyl-1,2,4-oxadiazole-5-carbonyl)-propyl]-butyramide; 2-(2-Morpholin-4-yl-2-oxo-ethyl)-5-phenyl-pentanoic acid, (*S*)-1-(3-phenyl-1,2,4-oxadiazole-5-carbonyl)-propyl}-amide; *N*-[(1*S*)-1-(Benzooxazol-2-yl-hydroxy-methyl)-3-phenyl-propyl]-2-cyclopropylmethylsulfonylmethyl-4-morpholin-4-yl-4-oxo-butyramide; (*R*)-2-((*S*)-1-Hydroxy-2-morpholin-4-yl-2-oxo-ethyl)-5-phenyl-pentanoic acid, 1-(benzoxazole-2-carbonyl)-propyl]-amide; (*R*)-5-(2-Difluoromethoxy-phenyl)-2-((*S*)-1-hydroxy-2-morpholin-4-yl-2-oxo-ethyl)-pentanoic acid, 1-(benzoxazole-2-carbonyl)-propyl]-amide; and 4-Morpholin-4-yl-*N*-[1-(oxazole-2-carbonyl)-cyclopropyl]-4-oxo-2-benzylsulfonyl methyl -butyramide;

30 and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual

isomers and mixtures of isomers thereof; and the pharmaceutically acceptable salts and solvates of such compounds and the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof.

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13. The compound of claim 7 of Formula I(c):

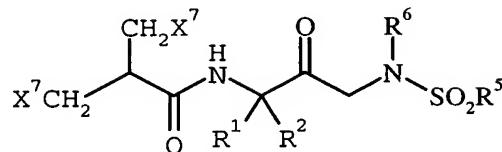


10 and the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof; and the pharmaceutically acceptable salts and solvates of such compounds and the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof.

15 14. The compound of claim 13 in which R⁵ is phenyl; and the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof; and the pharmaceutically acceptable salts and solvates of such compounds and the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof.

20 15. The compound of claim 14 selected from the group consisting of N-[(S)-1-((E)-2-benzenesulfonyl-vinyl)-pentyl]-3-benzenesulfonyl-2-benzenesulfonylmethyl-propionamide and N-(3-benzenesulfonyl-1-phenethyl-allyl)-3-benzenesulfonyl-2-benzenesulfonylmethyl-propionamide; and the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof; and the pharmaceutically acceptable salts and solvates of such compounds and the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof.

16. The compound of claim 7 of Formula I(d):



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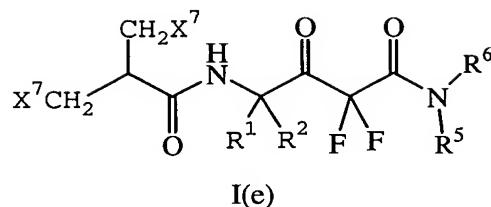
I(d)

and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof; and the pharmaceutically acceptable salts and solvates of such compounds and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof.

17. The compound of claim 16 in which R⁵ is phenyl and R⁶ is hydrogen; and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof; and the pharmaceutically acceptable salts and solvates of such compounds and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof.

18. The compound of claim 17 namely *N*-(3-benzenesulfonylamino-2-oxo-propyl)-4-morpholin-4-yl-4-oxo-2-benzylsulfonylmethyl-butyramide; and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof; and the pharmaceutically acceptable salts and solvates of such compounds and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof.

25 19. The compound of claim 7 of Formula I(e):



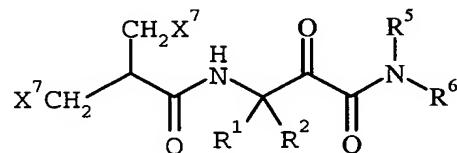
and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers
 5 and mixtures of isomers thereof; and the pharmaceutically acceptable salts and solvates of such compounds and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof.

20. The compound of claim 19 in which R⁵ and R⁶ is methyl;
 10 and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof; and the pharmaceutically acceptable salts and solvates of such compounds and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof.

15 21. The compound of claim 20 in which one X⁷ is morpholine-4-carbonyl and the other is benzylsulfonyl, R¹ is hydrogen and R² is ethyl, namely (S)-2,2-difluoro-4-(4-morpholin-4-yl-4-oxo-2-benzylsulfonylmethyl-butanoyleamino)-3-oxo-hexanoic acid dimethylamide;

and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof; and the pharmaceutically acceptable salts and solvates of such compounds and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof.

22. The compound of claim 7 of Formula I(f):
 25



I(f)

and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof; and the pharmaceutically acceptable salts and solvates of such compounds and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof.

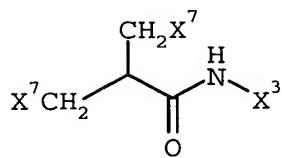
23. The compound of claim 22 in which R^5 is methyl, benzyl, phenethyl, cyclohexyl, methoxyethyl, dimethylaminoethyl, tetrahydro-pyran-4-yl, 1-methylsulfonyl-piperidin-4-yl, 4-methyl-piperazin-1-yl, morpholin-4-ylethyl, pyridin-2-yl, pyridin-2-ylmethyl or oxazol-2-ylmethyl; R^6 is hydrogen or methyl; or R^5 and R^6 together with the nitrogen atom to which both R^5 and R^6 are attached form morpholine-4-yl, pyrrolidin-1-yl, 4-dimethylamino-piperazin-1-yl, 4-hydroxy-piperazin-1-yl, 4-pyridin-2-yl-piperazin-1-yl, 4-benzoyl-piperazin-1-yl or 3-oxo-piperazin-1-yl;

15 and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof; and the pharmaceutically acceptable salts and solvates of such compounds and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof.

20 24. The compound of claim 23 selected from the group consisting of *N*-[(S)-1-(1-Benzylcarbamoyl-methanoyl)-propyl]-3-benzylsulfonyl-2-benzylsulfonylmethyl-propionamide and *N*-[(S)-1-(1-Benzylcarbamoyl-methanoyl)-propyl]-4-morpholin-4-yl-4-oxo-2-benzylsulfonylmethyl-butyramide;

25 and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof; and the pharmaceutically acceptable salts and solvates of such compounds and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof.

25. The compound of claim 7 of Formula I(g):



I(g)

and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers
 5 and mixtures of isomers thereof; and the pharmaceutically acceptable salts and solvates of such compounds and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof.

26. The compound of claim 25 in which X^3 is 1-benzoyl-4-oxo-pyrrolidin-3-yl,
 10 4-oxo-pyrrolidin-3-yl-1-carboxylic acid tert-butyl ester, 2-methyl-4-oxo-tetrahydro-furan-3-yl, 2-ethyl-4-oxo-tetrahydro-furan-3-yl, 4-oxo-tetrahydro-furan-3-yl, 2-acetoxy-4-oxo-azetidin-3-yl, 1-isopropyl-3-oxo-azepan-4-yl, 3-oxo-azepan-4-yl-1-carboxylic acid benzyl ester, 3-oxo-azepan-4-yl-1-carboxylic acid tert-butyl ester, 1-benzoyl-3-oxo-azepan-4-yl, 1-isobutyryl-3-oxo-azepan-4-yl, 3-oxo-1-(propane-2-sulfonyl)-azepan-4-yl, 1-benzenesulfonyl-3-oxo-azepan-4-yl, 1-benzenesulfonyl-3-oxo-piperidin-4-yl, 1-benzenesulfonyl-4-oxo-pyrrolidin-3-yl, 1-benzoyl-3-oxo-piperidin-4-yl or 3-oxo-tetrahydro-pyran-4-yl;

and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof; and the pharmaceutically acceptable salts and
 20 solvates of such compounds and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof.

27. The compound of claim 23 selected from the group consisting of 3-Hydroxy-4-(4-morpholin-4-yl-4-oxo-2-benzylsulfonylmethyl-butyrylamino)-azepane-1-carboxylic acid tert-butyl ester; 4-(2-Cyclopropylmethylsulfonylmethyl-4-morpholin-4-yl-4-oxo-butyrylamino)-3-hydroxy-azepane-1-carboxylic acid tert-butyl ester; 3-Hydroxy-4-[2-(2-methyl-propane-1-sulfonylmethyl)-4-morpholin-4-yl-4-oxo-butyrylamino]-azepane-1-carboxylic acid tert-butyl ester; 4-(4-Morpholin-4-yl-4-oxo-2-benzylsulfonylmethyl-

butyrylamino)-3-oxo-azepane-1-carboxylic acid tert-butyl ester; 4-(2-Cyclopropylmethylsulfonylmethyl-4-morpholin-4-yl-4-oxo-butyrylamino)-3-oxo-azepane-1-carboxylic acid tert-butyl ester; 4-[2-(2-Methyl-propane-1-sulfonylmethyl)-4-morpholin-4-yl-4-oxo-butyrylamino]-3-oxo-azepane-1-carboxylic acid tert-butyl ester; *N*-(1-5 Benzenesulfonyl-3-oxo-azepan-4-yl)-4-morpholin-4-yl-4-oxo-2-benzylsulfonylmethylbutyramide; *N*-(1-Benzenesulfonyl-3-oxo-azepan-4-yl)-2-(2-methyl-propane-1-sulfonylmethyl)-4-morpholin-4-yl-4-oxo-butyramide; 3-(4-Morpholin-4-yl-4-oxo-2-benzylsulfonylmethyl-butyrylamino)-4-oxo-pyrrolidine-1-carboxylic acid tert-butyl ester; 4-(4-Morpholin-4-yl-4-oxo-2-benzylsulfonylmethyl-butyrylamino)-3-oxo-azepane-1-carboxylic acid benzyl ester; and acetic acid (2*S*,3*S*)-3-(4-morpholin-4-yl-4-oxo-2-benzylsulfonylmethyl-butanoylamino)-4-oxo-azetidin-2-yl ester; and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof; and the pharmaceutically acceptable salts and solvates of such compounds and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof.

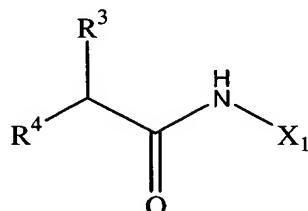
28. A pharmaceutical composition comprising a therapeutically effective amount of a compound of Claim 1 in combination with a pharmaceutically acceptable excipient.

20

29. A method for treating a disease in an animal in which inhibition of Cathepsin S can prevent, inhibit or ameliorate the pathology and/or symptomology of the disease, which method comprises administering to the animal a therapeutically effective amount of compound of Claim 1 or a *N*-oxide derivative or individual isomer or mixture of isomers thereof; or a pharmaceutically acceptable salt or solvate of such compounds and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof.

30. The use of a compound of Claim 1 in the manufacture of a medicament for treating a disease in an animal in which Cathepsin S activity contributes to the pathology and/or symptomology of the disease.

31. A process for preparing a compound of Formula I:



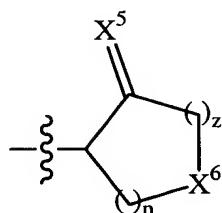
I

5

in which:

X^1 is $-C(R^1)(R^2)X^2$ or $-X^3$;
 X^2 is cyano, $-CHO$, $-C(R^7)(R^8)R^5$, $-C(R^7)(R^8)CF_3$, $-C(R^7)(R^8)CF_2CF_2R^9$,
 $-CH=CHS(O)_2R^5$, $-C(R^7)(R^8)CF_2C(O)NR^5R^6$, $-C(R^7)(R^8)C(R^7)(R^8)NR^5R^6$,
10 $-C(R^7)(R^8)C(R^7)(R^8)OR^5$, $-C(R^7)(R^8)CH_2OR^5$, $-C(R^7)(R^8)CH_2N(R^6)SO_2R^5$,
 $-C(R^7)(R^8)C(R^7)(R^8)N(R^6)(CH_2)_2OR^6$, $-C(R^7)(R^8)C(R^7)(R^8)N(R^6)(CH_2)_2NR^6$ or
 $-C(R^7)(R^8)C(R^7)(R^8)R^5$; wherein R^5 is (C_{1-4}) alkyl, (C_{6-10}) aryl(C_{0-6})alkyl,
hetero(C_{4-10})aryl(C_{0-6})alkyl, (C_{4-10}) cycloalkyl(C_{0-6})alkyl or
hetero(C_{4-10})cycloalkyl(C_{0-6})alkyl; R^6 is hydrogen or (C_{1-6}) alkyl; R^7 is hydrogen or
15 (C_{1-4}) alkyl and R^8 is hydroxy or R^7 and R^8 together form oxo; R^9 is hydrogen, halo,
 (C_{1-4}) alkyl, (C_{5-10}) aryl(C_{0-6})alkyl or hetero(C_{5-10})aryl(C_{0-6})alkyl;

X^3 represents a group of Formula (a):



20

(a)

in which n is 1 or 2, z is 0 or 1, X^5 is selected from NR^{10} , S or O, wherein R^{10} is hydrogen or (C_{1-6})alkyl, and X^6 is O, S or NR^{11} , wherein R^{11} is selected from hydrogen, (C_{1-6})alkyl, $-X^4C(O)OR^{12}$, $-X^4C(O)R^{13}$, $-X^4C(O)NR^{12}R^{12}$, $-X^4S(O)_2NR^{12}R^{12}$, $-X^4S(O)_2R^{14}$, $-R^{15}$, $-X^4S(O)_2R^{15}$, $-X^4C(O)R^{15}$, $-X^4C(O)OR^{15}$, $-X^4C(O)NR^{12}R^{15}$ and $-X^4S(O)_2NR^{12}R^{15}$, in which

5 X^4 is a bond or (C_{1-6})alkylene; R^{12} at each occurrence independently is hydrogen or (C_{1-6})alkyl; R^{13} is hydrogen, (C_{1-6})alkyl or halo-substituted(C_{1-6})alkyl, R^{14} is (C_{1-6})alkyl or halo-substituted(C_{1-6})alkyl and R^{15} is (C_{3-10})cycloalkyl(C_{0-6})alkyl, hetero(C_{3-10})cycloalkyl(C_{0-3})alkyl, (C_{6-10})aryl(C_{0-6})alkyl, hetero(C_{5-10})aryl(C_{0-6})alkyl, (C_{9-12})bicycloaryl(C_{0-6})alkyl or hetero(C_{8-12})bicycloaryl(C_{0-6})alkyl;

10 wherein within X^1 any cycloalkyl, heterocycloalkyl, aryl or heteroaryl may be substituted with 1 radical R^{20} selected from $-R^{15}$, $-X^4OR^{15}$, $-X^4SR^{15}$, $-X^4S(O)R^{15}$, $-X^4S(O)_2R^{15}$, $-X^4C(O)R^{15}$, $-X^4C(O)OR^{15}$, $-X^4OC(O)R^{15}$, $-X^4NR^{15}R^{12}$, $-X^4NR^{12}C(O)R^{15}$, $-X^4NR^{12}C(O)OR^{15}$, $-X^4C(O)NR^{15}R^{12}$, $-X^4S(O)_2NR^{15}R^{12}$, $-X^4NR^{12}S(O)_2R^{15}$, $-X^4NR^{12}C(O)NR^{15}R^{12}$ and $-X^4NR^{12}C(NR^{12})NR^{15}R^{12}$; and wherein X^1 and R^{20} may be

15 substituted further with 1 to 5 radicals independently selected from (C_{1-6})alkyl, cyano, halo, halo-substituted(C_{1-4})alkyl, nitro, $-X^4NR^{12}R^{12}$, $-X^4NR^{12}C(O)R^{12}$, $-X^4NR^{12}C(O)OR^{12}$, $-X^4NR^{12}C(O)NR^{12}R^{12}$, $-X^4NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^4OR^{13}$, $-X^4SR^{13}$, $-X^4C(O)OR^{12}$, $-X^4C(O)R^{13}$, $-X^4OC(O)R^{13}$, $-X^4C(O)NR^{12}R^{12}$, $-X^4S(O)_2NR^{12}R^{12}$, $-X^4NR^{12}S(O)_2R^{13}$, $-X^4P(O)(OR^{12})OR^{12}$, $-X^4OP(O)(OR^{12})OR^{12}$, $-X^4S(O)R^{14}$ and $-X^4S(O)_2R^{14}$ wherein X^4 , R^{12} ,

20 R^{13} , R^{14} and R^{15} are as defined above;

R^1 and R^2 are both fluoro; or

R^1 is hydrogen or (C_{1-6})alkyl and R^2 is selected from the group consisting of hydrogen, (C_{1-6})alkyl, cyano, $-X^4NR^{12}R^{12}$, $-X^4NR^{12}C(O)R^{12}$, $-X^4NR^{12}C(O)OR^{12}$, $-X^4NR^{12}C(O)NR^{12}R^{12}$, $-X^4NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^4OR^{13}$, $-X^4SR^{13}$, $-X^4C(O)OR^{12}$, $25 -X^4C(O)R^{13}$, $-X^4OC(O)R^{13}$, $-X^4C(O)NR^{12}R^{12}$, $-X^4S(O)_2NR^{12}R^{12}$, $-X^4NR^{12}S(O)_2R^{13}$, $-X^4P(O)(OR^{12})OR^{12}$, $-X^4OP(O)(OR^{12})OR^{12}$, $-X^4S(O)R^{14}$, $-X^4S(O)_2R^{14}$, $-R^{15}$, $-X^4OR^{15}$, $-X^4SR^{15}$, $-X^4S(O)R^{15}$, $-X^4S(O)_2R^{15}$, $-X^4C(O)R^{15}$, $-X^4C(O)OR^{15}$, $-X^4OC(O)R^{15}$, $-X^4NR^{15}R^{12}$, $-X^4NR^{12}C(O)R^{15}$, $-X^4NR^{12}C(O)OR^{15}$, $-X^4C(O)NR^{15}R^{12}$, $-X^4S(O)_2NR^{15}R^{12}$, $-X^4NR^{12}S(O)_2R^{15}$, $-X^4NR^{12}C(O)NR^{15}R^{12}$ and $-X^4NR^{12}C(NR^{12})NR^{15}R^{12}$, wherein X^4 , R^{12} ,

30 R^{13} , R^{14} and R^{15} are as defined above; or R^1 and R^2 taken together with the carbon atom to which both R^1 and R^2 are attached form (C_{3-8})cycloalkylene or hetero(C_{3-8})cycloalkylene;

wherein R^2 , said cycloalkylene and said heterocycloalkylene may be substituted further with 1 to 3 radicals independently selected from $(C_{1-6})alkyl$, cyano, halo, halo-substituted($C_{1-4}alkyl$), nitro, $-X^4NR^{12}R^{12}$, $-X^4NR^{12}C(O)R^{12}$, $-X^4NR^{12}C(O)OR^{12}$, $-X^4NR^{12}C(O)NR^{12}R^{12}$, $-X^4NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^4OR^{13}$, $-X^4SR^{13}$, $-X^4C(O)OR^{12}$, $-X^4C(O)R^{13}$, $-X^4OC(O)R^{13}$, $-X^4C(O)NR^{12}R^{12}$, $-X^4S(O)_2NR^{12}R^{12}$, $-X^4NR^{12}S(O)_2R^{13}$, $-X^4P(O)(OR^{12})OR^{12}$, $-X^4OP(O)(OR^{12})OR^{12}$, $-X^4S(O)R^{14}$ and $-X^4S(O)_2R^{14}$, wherein X^4 , R^{12} , R^{13} and R^{14} are as defined above;

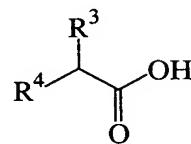
R^3 and R^4 are independently $-C(R^{16})(R^{17})X^7$, wherein R^{16} and R^{17} are hydrogen, $(C_{1-6})alkyl$ or fluoro, or R^{16} is hydrogen and R^{17} is hydroxy and X^7 is selected from $-X^4NR^{12}R^{12}$, $-X^4NR^{12}C(O)R^{12}$, $-X^4NR^{12}C(O)OR^{12}$, $-X^4NR^{12}C(O)NR^{12}R^{12}$, $-X^4NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^4OR^{13}$, $-X^4SR^{13}$, $-X^4C(O)OR^{12}$, $-X^4C(O)R^{13}$, $-X^4OC(O)R^{13}$, $-X^4C(O)NR^{12}R^{12}$, $-X^4S(O)_2NR^{12}R^{12}$, $-X^4NR^{12}S(O)_2R^{13}$, $-X^4P(O)(OR^{12})OR^{12}$, $-X^4OP(O)(OR^{12})OR^{12}$, $-X^4S(O)R^{14}$, $-X^4S(O)_2R^{14}$, $-R^{15}$, $-X^4OR^{15}$, $-X^4SR^{15}$, $-X^4S(O)R^{15}$, $-X^4S(O)_2R^{15}$, $-X^4C(O)R^{15}$, $-X^4C(O)OR^{15}$, $-X^4OC(O)R^{15}$, $-X^4NR^{15}R^{12}$, $-X^4NR^{12}C(O)R^{15}$, $-X^4NR^{12}C(O)OR^{15}$, $-X^4C(O)NR^{15}R^{12}$, $-X^4S(O)_2NR^{15}R^{12}$, $-X^4NR^{12}S(O)_2R^{15}$, $-X^4NR^{12}C(O)NR^{15}R^{12}$ and $-X^4NR^{12}C(NR^{12})NR^{15}R^{12}$, wherein X^4 , R^{12} , R^{13} , R^{14} and R^{15} are as defined above;

wherein within one of R^3 or R^4 any cycloalkyl, heterocycloalkyl, aryl or heteroaryl may be substituted with 1 radical R^{21} selected from $-R^{15}$, $-X^4OR^{15}$, $-X^4SR^{15}$, $-X^4S(O)R^{15}$, $-X^4S(O)_2R^{15}$, $-X^4C(O)R^{15}$, $-X^4C(O)OR^{15}$, $-X^4OC(O)R^{15}$, $-X^4NR^{15}R^{12}$, $-X^4NR^{12}C(O)R^{15}$, $-X^4NR^{12}C(O)OR^{15}$, $-X^4C(O)NR^{12}R^{15}$, $-X^4S(O)_2NR^{15}R^{12}$, $-X^4NR^{12}S(O)_2R^{15}$, $-X^4NR^{12}C(O)NR^{15}R^{12}$ and $-X^4NR^{12}C(NR^{12})NR^{15}R^{12}$, wherein X^4 , R^{12} and R^{15} are as defined above; and wherein each of R^3 , R^4 and R^{21} may be substituted further with 1 to 5 radicals independently selected from $(C_{1-6})alkyl$, cyano, halo, halo-substituted($C_{1-4}alkyl$), nitro, $-X^4NR^{12}R^{12}$, $-X^4NR^{12}C(O)R^{12}$, $-X^4NR^{12}C(O)OR^{12}$, $-X^4NR^{12}C(O)NR^{12}R^{12}$, $-X^4NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^4OR^{13}$, $-X^4SR^{13}$, $-X^4C(O)OR^{12}$, $-X^4C(O)R^{13}$, $-X^4OC(O)R^{13}$, $-X^4C(O)NR^{12}R^{12}$, $-X^4S(O)_2NR^{12}R^{12}$, $-X^4NR^{12}S(O)_2R^{13}$, $-X^4P(O)(OR^{12})OR^{12}$, $-X^4OP(O)(OR^{12})OR^{12}$, $-X^4S(O)R^{14}$ and $-X^4S(O)_2R^{14}$, wherein X^4 , R^{12} , R^{13} and R^{14} are as defined above; provided that only one bicyclic ring structure is present within each of R^3 or R^4 ; and provided that when X^2 is cyano and X^7 within one of R^3 or R^4 is $-X^4C(O)R^{13}$ or $-X^4C(O)R^{15}$, wherein X^4 is a bond, then X^7 within the other of R^3 or R^4 is limited to

-X⁴SR¹⁵, -X⁴S(O)R¹⁵ and -X⁴S(O)₂R¹⁵, wherein R¹⁵ is (C₆₋₁₀)aryl(C₁₋₆)alkyl substituted with 1 to 5 radicals or hetero(C₅₋₁₀)aryl(C₀₋₆)alkyl optionally substituted with 1 to 5 radicals, wherein said radicals are independently selected from (C₁₋₆)alkyl, cyano, halo, halo-substituted(C₁₋₄)alkyl, nitro, -X⁴NR¹²R¹², -X⁴NR¹²C(O)R¹², -X⁴NR¹²C(O)OR¹²,
5 -X⁴NR¹²C(O)NR¹²R¹², -X⁴NR¹²C(NR¹²)NR¹²R¹², -X⁴OR¹³, -X⁴SR¹³, -X⁴C(O)OR¹²,
-X⁴C(O)R¹³, -X⁴OC(O)R¹³, -X⁴C(O)NR¹²R¹², -X⁴S(O)₂NR¹²R¹², -X⁴NR¹²S(O)₂R¹³,
-X⁴P(O)(OR¹²)OR¹², -X⁴OP(O)(OR¹²)OR¹², -X⁴S(O)R¹⁴ and -X⁴S(O)₂R¹⁴, wherein X⁴, R¹²,
R¹³ and R¹⁴ are as defined above, provided that the radical is not selected from only halo
when R¹⁵ is (C₆₋₁₀)aryl(C₁₋₆)alkyl; and provided that when X² is cyano then X⁷ within R³
10 and R⁴ is not -X⁴C(O)NR¹²R¹², -X⁴C(O)NR¹⁵R¹² or -X⁴C(O)NR¹⁸R¹⁹, wherein X⁴ is a bond
and R¹⁸ and R¹⁹ together with the nitrogen atom to which they are attached form
hetero(C₃₋₁₀)cycloalkyl or hetero(C₅₋₁₀)aryl;

and the corresponding N-oxides, and their prodrugs, and their protected derivatives, individual isomers and mixtures of isomers thereof; and the pharmaceutically acceptable salts and solvates of such compounds of formula I and their N-oxides and their prodrugs, and their protected derivatives, individual isomers and mixtures of isomers thereof; which process comprises:

(A) reacting a compound of Formula 2:



20 with a compound of the formula NH₂CR¹R²X², in which X², R¹, R², R³ and R⁴ are as defined in the Summary of the Invention for Formula I; or

(B) reacting a compound of Formula 2 with a compound of the formula NH₂X³, in which X³, R³ and R⁴ are as defined in the Summary of the Invention for Formula I;

25 or

(C) optionally converting a compound of Formula I into a pharmaceutically acceptable salt;

(D) optionally converting a salt form of a compound of Formula I to non-salt form;

- (E) optionally converting an unoxidized form of a compound of Formula I into a pharmaceutically acceptable *N*-oxide;
- (F) optionally converting an *N*-oxide form of a compound of Formula I into its unoxidized form;
- 5 (G) optionally resolving an individual isomer of a compound of Formula I from a mixture of isomers;
- (H) optionally converting a non-derivatized compound of Formula I into a pharmaceutically prodrug derivative; and
- (I) 10 optionally converting a prodrug derivative of a compound of Formula I to its non-derivatized form.